

**REMARKS**

**A. The Status of the Claims and the Amendments**

Claims 1, 47, 49-51, and 55 are pending. By the present amendment, claim 1 has been amended to more particularly define the Applicant's invention and to claim it with greater specificity. As amended, the amendments to claim 1 are supported by the specification and the original claims. More specifically, claim 1 as amended now recites microspheres including an outer layer comprising a lipid and having a first surface and a second surface, and the inner layer disposed over the first surface of the outer layer. The outer layer is free of drugs and the inner layer comprises an oil and is free of a gas. The inner layer defines a void, the void containing a gas or gaseous precursor, the lipid comprises at least one phosphatidic acid and the therapeutic compound is dispersed within the inner layer.

Every limitation of claim 1 as amended is clearly shown on the original Figure 2. Indeed, Figure 2 depicts a microsphere formed by a doubled-layered shell, defining internal space filled with gas. The shell has an outer layer (lipid) and an inner layer (oil), the inner layer lining the outer layer. Finally, Figure 2 shows a drug dispersed throughout the inner oil layer. As shown, the inner layer does not include any gas, while the outer lipid layer includes no drugs. Accordingly, it is submitted that no new matter has been added by the amendments to claim 1. It is submitted that the amendments place the claims in condition for allowance. Entry of the amendments is respectfully requested.

**B. Rejection Under 35 U.S.C. § 102 (b)**

Claims 1, 47, 49-51, and 55 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,469,854 to Unger et al. (item 3 on pages 2-3 of the Office Action). This rejection is respectfully traversed.

It is well established that a valid rejection of a claim on the grounds of anticipation by a reference requires that the reference disclose all of the elements, limitations, and relationships recited in the claim. Such disclosure may be explicit or implicit. It is respectfully submitted that Unger et al. do not teach, either explicitly or implicitly all the elements and limitations of claim 1, as amended.

Specifically, Unger et al. teach gas-filled liposomes described in numerous places in the reference (see, e.g., abstract; col. 4, lines 44-45) having a lipid shell (col. 11, lines 40-50) and biologically active materials optionally incorporated into the lipid layer (col. 13, lines 18-24). Unger et al. fail to teach

“lipid microspheres including: (a) a drug-free outer layer comprising a lipid, the outer layer having a first surface and a second surface; and (b) a gas-free inner layer comprising an oil, the inner layer being disposed over the first surface of the outer layer, wherein the inner layer defines a void, the void containing a gas or gaseous precursor, wherein said lipid comprises at least one phosphatidic acid and the therapeutic compound is dispersed within the inner layer,”

as recited in claim 1, as amended. More specifically, Unger et al. fail to teach that liposomes include an oil layer disposed over the lipid layer. Indeed, the only use for oil described by Unger is as a stabilizer, viscosity modifier, emulsifier or solubilizing agent (see, col. 13, lines 25-33) or as a carrier for administration of the gas-filled liposomes (col. 18, lines 7-21). Clearly, then, oil in Unger et al. is present outside the microspheres, not inside them, as required by claim 1, as amended. Nor is there any teaching in Unger et al. that a drug that is present is dispersed in the oil, as required by claim 1, as amended. To the contrary, the only way of incorporating the therapeutic agent described by Unger et al. is ensconcing the drug in the lipid layer, as discussed above, while claim 1, as amended, specifically requires to have a drug-free lipid layer.

In view of the foregoing, claim 1, as amended, is patentably distinguishable over Unger et al. Each of claims 47, 49-51 and 55 depends on claim 1, directly or indirectly, and is considered patentable for at least the same reason. Withdrawal of the rejection and reconsideration are respectfully requested.

**C. Rejection Under 35 U.S.C. § 103(a)**

Claims 1, 47, 49-51, and 55 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,498,421 to Grinstaff et al. in view of Unger et al. or in view of U.S. Patent No. 4,960,595 to Hirota et al. (item 4 on page 4 of the Office Action). This rejection is respectfully traversed on the following grounds.

It is settled law that to establish a *prima facie* case of obviousness, the following three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference as proposed by the Examiner; (2) there must be a reasonable expectation of success and (3) the prior art reference must teach or suggest all of the claim limitations. MPEP § 2143.

Grinstaff et al. disclose the use of polymeric shells encapsulating a biologic agent. The shells are made of a protein, and the use of biologic polymers such as albumin is preferred (see, col. 9, lines 1-4). Grinstaff et al. further disclose that a fluorinated gas and an oil can be contained within the polymeric shells (see, FIG. 1 and col. 7, lines 34-35). Grinstaff et al. fail to describe shells made of

“a drug-free outer layer comprising a lipid ...  
and ... a gas-free inner layer comprising  
an oil, the inner layer being disposed over  
the first surface of the outer layer, wherein  
the inner layer defines a void, the void  
containing a gas or gaseous precursor”

as recited in claim 1, as amended. Indeed, in the liposomes described by Grinstaff et al. there is no separate inner layer made of oil and disposed over the lipid layer. In addition, in Grinstaff et al. there is no gas-filled void surrounded by the gas-free oil layer. To the

contrary, Grinstaff et al. teach that the oil and the gas are mixed (see FIG. 1, and the description of the interior B of the liposomes as provided by Grinstaff et al. in col. 7, lines 34-35). Accordingly, Grinstaff et al. fail to disclose every element of claim 1, as amended. Both Unger et al. and Hirota et al. fail to cure the deficiencies of Grinstaff et al.

Specifically, as discussed above, Unger et al. fail to describe or suggest a separate inner layer made of oil and disposed over the lipid layer. Nor do they describe or suggest a gas-filled void surrounded by the gas-free oil layer. Thus, even if the teachings of Grinstaff et al. and Unger et al. were to be combined, the combination still fails to disclose or suggest every limitation of claim 1, as amended.

Using the disclosure of Hirota et al. does not help to eliminate the above-discussed deficiencies. Indeed, all Hirota et al. teach is lipid membrane structures containing a lactose monofatty acid ester or amide (abstract ) where some phosphatidic acids can be used for forming the membrane (col. 3, lines 10-15). There is nothing in Hirota et al. describing a double-layer shell comprising separate lipid and oil layers, encapsulating a gas, and having a drug dispersed in the oil layer but not in the lipid layer, as required by claim 1, as amended. Accordingly, even if the teachings of Grinstaff et al. and Hirota et al. or of Grinstaff et al., Unger et al., and Hirota et al. were to be combined, the combination of all three references neither explicitly teaches nor implicitly suggests every limitation of claim 1, as amended.

In view of the foregoing, claim 1, as amended, is patentably distinguishable over Grinstaff et al. in view of Unger et al., or over Grinstaff et al. in view of Hirota et al. Or over any combination of these three references. Each of claims 47, 49-51 and 55 depends on claim 1, directly or indirectly, and is considered patentable for at least the same reason. Withdrawal of the rejection and reconsideration are respectfully requested.

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**CONCLUSION**

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

No fee is deemed to be due in connection with this response. However, if any fee is due, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

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